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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09 815,944	03 22 2001	Keith D. Allen	R-654	8251

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EXAMINER

QIAN, CELINE X

ART UNIT PAPER NUMBER

1636

DATE MAILED: 03/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/815,944

Applicant(s)

ALLEN ET AL.

Examiner

Celine Qian

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 19 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 11-16 and 22-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 17-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Claims 1-25 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the inventions in Groups I-VI are related and thus a search can be made without serious burden on the Examiner. Specifically, Applicants argue that the methods of Groups II and III, II and V, III and V share a common starting material, the transgenic knockout mouse, therefore, the inventions are related. Applicants further argue that the method of Group II can produce the products of Group VI. This is not found persuasive because of the following reasons. While the Examiner agrees with Applicants' arguments with regard to Groups II and III, II and V, III and V that they share a common starting material, the transgenic knockout mouse, however, is not the only starting material in these methods. The agents being tested are also part of starting material and they are different for each group. For instance, an agent that modulates the expression of a gene is different from an agent that modulates the function of said gene. Regarding to Groups II and VI, an agent that ameliorates a hypoactive behavior is not necessary able to modulating melanocyte stimulating hormone receptor expression. In addition, said agent can also be identified using animals exhibiting hypoactive behavior rather than the transgenic knockout mouse as recited. Therefore, the inventions of Groups I-VI are patentably distinct for the same reasons set forth in the prior office action mailed on 12/31/01. The Examiner agrees that the inventions are related, the inventions are patentably distinct however, and the search as required for the different groups are not co-extensive. Therefore, a search of all the groups will be a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-16 and 22-25 are withdrawn from consideration as being drawn to non-elected inventions. Claims 1-10 and 17-21 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a melanocyte stimulating hormone receptor gene knockout mouse exhibiting the phenotype of hypoactive behavior, does not reasonably provide enablement for any other melanocyte stimulating hormone receptor gene knockout non-human animals without said phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention is a melanocyte stimulating hormone receptor gene knockout non-human animal. The specification discloses the generation of a mouse having melanocyte stimulating hormone receptor gene disrupted by homologous recombination in mouse ES cells and said mouse exhibit the phenotype of hypoactive behavior (see page 59).

Since homologous recombination is required for gene targeting method as employed by the specification, embryonic stem cell technology must be available to carry out the method. At the time of the invention, no embryonic stem cell other than mouse was isolated as indicated by the art (Osterrieder & Wolf, Rev. sci. tech. Off. int. Epiz., vol. 17, no. 1, 351-364, 1998). The

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guidance of specification is limited and does not provide a method as to obtain ES cells from other animals. The specification only teaches generation of a melanocyte stimulating hormone receptor gene knockout mouse by using ES cells containing disrupted melanocyte stimulating hormone receptor gene achieved by homologous recombination. The specification does not teach the generation of ES cells of other non-human animals. Further the specification does not teach the generation of a melanocyte stimulating hormone receptor gene knockout non-human animal by other methods. Lack of guidance from specification, one skilled in the art would turn to prior art for guidance to make a melanocyte stimulating hormone receptor gene knockout non-human animal other than mouse. However, the prior art does not teach gene targeting methods other than homologous recombination. The art does not teach how to generate embryonic stem cells from non human animals other than mouse. Therefore, one skilled in the art would have to engage in undue amount of experimentation to make the claimed invention, a melanocyte stimulating hormone receptor gene knockout non-human animal.

Claims 8 do not recite any particular phenotype for a transgenic non-human animal comprising a disruption in a melanocyte stimulating hormone receptor gene. However, the phenotype exhibited by the melanocyte stimulating hormone receptor gene knockout non-human animal as a consequence of gene knockout, as disclosed in the specification, is required to enable the use of the non-human animal to identify agents that ameliorates hypoactive behavior, for example. The specification does not teach how to use the non-human animals lacking this phenotype. Therefore, one skilled in the art would have to engage in undue amount of experimentation to use the claimed invention.

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous melanocyte stimulating hormone receptor gene knockout mouse lacks production of functional melanocyte stimulating hormone receptor, does not reasonably provide enablement for a heterozygous melanocyte stimulating hormone receptor knockout mouse or a melanocyte stimulating hormone receptor gene disrupted mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is a transgenic mouse comprising a disruption in a melanocyte stimulating hormone receptor gene and exhibits phenotype comprising hypoactive behavior; and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using a melanocyte stimulating hormone receptor targeting construct (see page 54-59, examples 1-4). The specification further discloses that the homozygous knockout mice exhibit the phenotype comprising lymphocytes infiltration in lung, pancreas, stomach and liver (see page 62, lines 8-24).

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg. 1425, col. 1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol 20:1425-1429). The specification discloses the phenotype of a homozygous melanocyte stimulating hormone receptor knockout mouse. Claims 17, 18 and 20 encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be

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expected to have the same phenotype as the homozygotes. Thus, the phenotype of a melanocyte stimulating hormone receptor knockout mouse is unpredictable.

The specification discloses that the word "disruption" comprises alter or replace a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal product's activity (see page 7, lines 12-15). However, it is not known in the prior art that such "disruption," would produce the phenotype as disclosed by the specification. The specification only discloses a mouse with two alleles of melanocyte stimulating hormone receptor disrupted by inserting a selection marker that exhibits the phenotype comprising hypoactive behavior. Thus, the phenotype of a transgenic mouse comprising a "disruption," as defined by the specification, in a melanocyte stimulating hormone receptor gene is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic knockout mouse that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. As such, the metes and bounds of the claim cannot be established.

Regarding claims 9 and 21, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Claim 21 recites "the transgenic mouse of claim 20," however, claim 20 is drawn to a method of producing transgenic mouse. Thus, claim 21 is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Cone et al.(US 6,278,038).

The claims are drawn to a melanocyte stimulating hormone receptor gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a melanocyte stimulating hormone receptor, a transgenic non-human animal comprising a disruption in a melanocyte stimulating hormone receptor, and a method of

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producing a transgenic mouse comprising a disruption in a melanocyte stimulating hormone receptor gene by homologous recombination using the target construct.

Cone et al. disclose the generation of a melanocyte stimulating hormone receptor knockout mouse by homologous recombination using a targeting construct (see col. 22-30, example 4 and 5) and subsequent analysis of phenotype of said mouse. Cone et al. also disclose that immortalized cell line can be derived from tissues and organs of said knockout mouse. Therefore, Cone et al. disclose the instant claimed inventions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Mountjoy et al. (1992, Science vol. 257, 1248-1251) and Adachi et al (1999, J. Immunology, vol. 163: 3363-3368).

The claims are drawn to a melanocyte stimulating hormone receptor gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a melanocyte stimulating hormone receptor gene, and a method of producing a transgenic mouse comprising a disruption in a melanocyte stimulating hormone receptor gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from *hprt* and *int-2* respectively, and a neo selection marker in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a melanocyte stimulating hormone receptor gene target construct and knockout mouse.

Mountjoy et al. teach the cloning of mouse melanocyte stimulating hormone receptor gene. They provide the cloned coding sequence for melanocyte stimulating hormone receptor gene (see page 1249, figure 2 legend, accession number X65633-5).

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Adachi et al. teach that melanocyte stimulating hormone receptor is expressed on a stimulated mast cell line and melanocyte stimulating hormone alpha inhibits histamine release from mast cells (see page 3367, col. 1, lines 4-16). Adachi et al. also teach that melanocyte stimulating hormone alpha may be involved in stimulating cell proliferation in the presence of IL-3 (see page 3367, 2nd col. Lines 7-11). Adachi et al. further teach that melanocyte stimulating hormone alpha affects cytokine production in inflammatory tissue (3367, 2nd col., 2nd paragraph).

It would have been obvious to one in the ordinary art to make a melanocyte stimulating hormone receptor knockout mouse. The ordinary artisan would have been motivated to knockout the function of melanocyte stimulating hormone receptor gene in a mouse to study the role melanocyte stimulating hormone alpha plays in cell proliferation and tissue inflammatory response (3367, 2nd col., 2nd paragraph). The ordinary artisan would have had reasonable expectation of success because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Mountjoy et al., who teach the coding sequence of the mouse melanocyte stimulating hormone receptor gene, and Adachi et al., who teach the importance of this gene in regulating cell proliferation and cytokine production in inflammatory response. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian Ph.D.
March 15, 2002


REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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